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THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE
(Project Description)

Request to the Office of Naval Research for Renewal of

Contract NR 113-149
Serial 18249
Naonr 181-53

I. Background Information

Since July 1951, a project designed to develop a synthetic drug which would be as safe as codeine with respect to toxicity, antitussive activity, and addiction liability has been carried on within the National Institute of Mental Health Addiction Research Center, PHS Hospital, Lexington, Kentucky. This project has been financed in large part by funds from the Office of Naval Research and this description constitutes a request for renewal of the project for the period 1 July 1956 to 30 June 1957.

A synthetic substitute for codeine is badly needed since opium or morphine derived from opium constitute the only source of codeine. Unless a synthetic substitute for codeine is developed the United States must continue to stockpile opium in order to provide adequate supplies of codeine for both the civilian and military populations in the event of war. The facilities of the NIMH Addiction Research Center are not sufficient to carry on this work in addition to drug testing

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required for the evaluation of all new analgesics, unless additional funds are supplied by the Department of Defense.

2. Work Accomplished to Date

Previous work has been summarized in the annual progress reports sent to Capt. F. H. Quimby, Head of the Physiology Branch, Office of Naval Research.

Two drugs have been developed which are promising potential substitutes for codeine for relief of cough. These drugs are (1) dextromethorphan, and (2) narcotine. Neither drug possesses any addiction liability and both have relatively low toxicity. They currently are under intensive clinical study for antitussive effect.

Although two very promising antitussive substitutes for codeine have been found, no compound is yet available which is as effective as codeine for the relief of mild grades of pain and which is as safe as codeine with respect to both toxicity and addiction liability. More than 25 compounds have been studied to date. Seven of these compounds have some promise as substitutes for codeine for analgesic use. The outstanding compounds are alpha-dl- and alpha-d-1,2-Diphenyl-2-propionoxy-dimethylamino-3-methylbutane. The dextrorotatory isomer accounts for all the analgesic potency of these particular compounds. The drugs are nontoxic, are better sedatives than

is codeine, suppresses abstinence from morphine only slightly, and have been reported to be effective in the relief of clinical pain, although studies of the analgesic effect are still inadequate.

3. Need for Continuation of the Project

Although two drugs have been discovered that have promise as potential antitussive substitutes for codeine and several drugs have been discovered which might serve as possible substitutes for codeine for analgesia, it is still unknown whether any of these drugs will be completely satisfactory for clinical use for either purpose. It is, therefore, essential to continue the search since the larger the number of compounds developed greater is the chance of finding a completely adequate substitute.

4. Work Proposed

During the period 1 July 1956 to 30 June 1957 we propose to complete the studies on the very important methylbutane compounds mentioned above. This drug is so promising that direct addiction liability studies are required. Such studies are very time consuming and will require six to nine months for completion. In addition, we intend to study the addiction liability of N-allyldihydrohydroxycodone to evaluate the

addiction liability of the dihydrocodeine and to study such other substances as may be suggested by the Committee on Drug Addiction and Narcotics, National Research Council.

5. Methods

The methods to be used are the standard addiction liability testing methods of the NIMH Addiction Research Center. These have been described in previous project descriptions and should be consulted for details.

6. Evaluation of Data

The evaluation of data obtained in the addiction liability program has also been discussed in previous project descriptions.

7. Location of Project

Work will be carried out at the NIMH Addiction Research Center, PHS Hospital, Lexington, Kentucky. This institution provides the two necessary facilities for the type of work to be undertaken: (1) a pool of patients who will volunteer for experiments with drugs, and (2) strict environmental control which prevents the introduction of drugs other than those under study into the experimental situation.

8. Experimental Personnel

Work will be carried out under the direction of Harris Isbell, M.D., Director, NIMH Addiction Research Center. This investigator has had twelve years of experience in research in narcotic drug addiction and has published many papers in the field. He will be assisted by two other experienced physicians, Dr. H. F. Fraser and Dr. Abraham Wikler, both of whom have had extensive experience in research in addiction, with many publications. In addition to these medical personnel the part-time services of a biochemist and research psychologist will be made available. A special ward for the conduct of these studies is currently in operation.

9. Estimated Cost

The amount of money requested has been increased. This is necessary in order to provide funds for the increase in Civil Service pay which went into effect in March 1955.

1. Personnel

6 Psychiatric Aides GS-5 (\$4210. p.a.)
1 Physical Science Aide GS-5

2. Reserve for Premium Pay
(Night differential, Holiday, Overtime)

3. Travel

4. Miscellaneous Expense
(Drugs, chemicals, glassware,
photographic supplies, etc)

Total-----

H:rn
23 January 1956

Harris Isbell, M.D.
Director

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